**NAME OF THE MEDICINE**

Perindopril arginine and Amlodipine besylate

**Perindopril Arginine**

Chemical Name: \( (2S,3aS,7aS)-1-[(2S)-2-[[1S]-1-\text{[Ethoxycarbonyl]butyl}amino]propanoyl]octahydro-1H-indole-2-carboxylic acid, L-arginine salt. \)

Structural Formula:

![Perindopril Arginine Structural Formula](image)

Molecular Formula: \( C_{19}H_{32}N_2O_5 \cdot C_6H_{14}N_4O_2 \)

Molecular Weight: 542.67

CAS Registry Number: 612548-45-5

**Amlodipine Besylate**

Chemical Name: \( 3\)-ethyl \( 5\)-methyl \((4RS)-2-[[2\text{-aminoethoxy}]methyl]-4-(2\text{-chlorophenyl})-6-methyl-1,4\text{-dihydropyridine-3,5-dicarboxylate benzenesulfonate} \)

Structural Formula:

![Amlodipine Besylate Structural Formula](image)

Molecular Formula: \( C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S \)

Molecular Weight: 567.1 (free base 408.9)

CAS Registry Number: 111470-99-6
DESCRIPTION

Perindopril arginine has the chemical name, L-arginine (2S, 3aS, 7aS)-1-N-[(S)-1-ethoxycarbonyl butyl]-L-alanyl perhydroindole-2-carboxylate. It is a dipeptide monoacid monoester with a perhydroindole group and no sulphhydryl radical. Perindopril arginine is a white powder, readily soluble in purified water, slightly soluble in 95% ethanol and practically insoluble in chloroform. Perindopril has five asymmetric centres. The drug is synthesised stereoselectively so that it is a single enantiomer (all S stereochemistry).

Amlodipine besylate is a dihydropyridine derivative, and has the following chemical name: 3-ethyl 5-methyl-2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate benzene sulphonate. Amlodipine besylate is chiral and present as a racemate. It is a white crystalline powder and is slightly soluble in water and sparingly soluble in ethanol. It has a molecular weight of 567.1 (free base 408.9).

Perindopril arginine and amlodipine combination tablets contains the following amount of perindopril arginine and amlodipine (as besylate) respectively: 5mg/5mg, 5mg/10mg, 10mg/5mg & 10mg/10mg. In addition, each tablet contains the following inactive ingredients: microcrystalline cellulose, croscarmellose sodium, colloidal anhydrous silica and magnesium stearate.

PHARMACOLOGY

Pharmacological Actions

Related to Perindopril

Perindopril (prodrug), following hydrolysis to perindoprilat, inhibits angiotensin converting enzyme (ACE) both in vitro and in vivo. It is thought that ACE inhibitors reduce blood pressure by inhibiting the enzyme which catalyses the conversion of angiotensin I to angiotensin II. Decreased plasma angiotensin II leads to increased plasma renin activity and a decrease in aldosterone. In addition to its effects on circulating ACE, perindopril binds to and inhibits tissue converting enzyme, predominantly in the kidney and vascular wall. The contribution of this mechanism to the overall antihypertensive effect of perindopril is unknown. Animal studies have demonstrated reversal of vascular hypertrophy and an improvement in the ratio of elastin to collagen in the vessel wall. Studies in man have demonstrated an improvement in the visco-elastic properties of large vessels and in compliance. Studies in animals and humans suggest that specific and competitive suppression of the renin-angiotensin-aldosterone system is the main mechanism by which blood pressure is reduced. However, antihypertensive activity has also been observed in patients with low renin activity. Perindopril may also inhibit the degradation of the potent vasodepressor peptide, bradykinin, and this action may contribute to its antihypertensive action. Perindopril appears to reduce peripheral resistance and may influence arterial compliance.

Related to Amlodipine

Amlodipine is a calcium ion influx inhibitor (slow channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle.

Experimental data suggest that amlodipine binds to both dihydropyridine and non-dihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Negative inotropic effects can be detected in vitro but such effects have not been seen in intact animals at therapeutic doses. Serum calcium concentration is not affected by amlodipine. Within the physiologic pH range, amlodipine is an ionized compound (pKa=8.6), and its kinetic interaction with the calcium channel receptor is characterised by a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect.

Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure. The precise mechanism by which amlodipine relieves angina has not been fully determined but amlodipine reduces the total ischaemic burden by the following two actions:

1. Amlodipine dilates peripheral arterioles and thus reduces the total peripheral resistance (afterload)
against which the heart works. Since the heart rate remains stable, this unloading of the heart reduces myocardial energy consumption and oxygen requirements.

2. Amlodipine has been shown to block constriction in main coronary arteries and coronary arterioles, induced by calcium, potassium, adrenaline, serotonin and thromboxane A2 analogue both in normal and in ischaemic regions.

Pharmacokinetics

Three studies have demonstrated bioequivalence between one tablet of the fixed combination of perindopril/amlodipine and the co-administration of one tablet of perindopril plus one tablet of amlodipine, at dose ranges equivalent to perindopril arginine/amlodipine tablet 5mg/10mg, perindopril arginine/amlodipine tablet 10mg/5mg and perindopril arginine/amlodipine tablet 10mg/10mg.

The results of these studies were similar across the different doses and demonstrated that the rate and extent of absorption of perindopril and amlodipine in perindopril arginine and amlodipine combination tablet are not significantly different, respectively, from the rate and extent of absorption of perindopril and amlodipine in individual tablet formulations.

A pharmacokinetic interaction study between perindopril arginine 10 mg and amlodipine 10 mg revealed that the extent and rate of bioavailability of perindopril, perindoprilat and amlodipine are similar for perindopril arginine 10 mg or amlodipine 10 mg administered alone or within a co-administration.

No pharmacokinetic interaction exists between these two formulations.

Related to Perindopril

Following oral administration, perindopril is rapidly absorbed with bioavailability of 24%. Elimination is rapid, occurring predominantly via the urine. Plasma half-life is approximately 1 hour. Bioavailability of the active metabolite perindoprilat is approximately 27%. Peak plasma concentrations of perindoprilat occur 3 to 4 hours after oral administration of perindopril. Protein binding of perindoprilat is 20%, principally to angiotensin converting enzyme. Perindoprilat binds to plasma and tissue ACE, and free perindoprilat is eliminated through the urine. The terminal half-life of the unbound fraction is approximately 17 hours. When perindopril is administered chronically, steady state of perindoprilat is reached within 4 days, and perindoprilat does not accumulate. Food intake may reduce hepatic biotransformation to perindoprilat. The elimination of perindoprilat is reduced in elderly patients and in patients with cardiac and renal failure. Apart from perindoprilat, the administration of perindopril leads to the formation of 5 other metabolites, all of which are inactive and exist in very low quantities. One of these is the glucurononconjugate of perindoprilat, which is formed by a hepatic first-pass effect. This effect does not appear to have any influence on the kinetics of perindoprilat.

Related to Amlodipine

After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6-12 hours post-dose. This may reflect significant initial uptake by the liver, followed by a phase of redistribution. This interval is shorter (2-8 hours) in patients with hepatic insufficiency. Absolute bioavailability has been estimated to be between 64 and 90%.

The bioavailability of amlodipine is not altered by the presence of food. The volume of distribution is approximately 20 L/kg. The terminal plasma elimination half-life is about 35 - 50 hours and is consistent with once daily dosing. Steady state plasma levels are reached after 7-8 days of consecutive dosing.

Amlodipine is extensively metabolised by the liver to inactive metabolites with 10% of the parent compound and 60% of metabolites excreted in the urine.

In elderly hypertensive patients (mean age 69 years) there was a decrease in clearance of amlodipine from plasma as compared to young volunteers (mean age 36 years) with a resulting increase in the area under the curve (AUC) of about 60%.

In vitro studies have shown that approximately 97.5% of circulating amlodipine is bound to plasma proteins.
In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow without change in filtration fraction or proteinuria.

**Pharmacodynamics**

*Related to Perindopril*

**Hypertension**

Studies carried out in animal models of hypertension have shown that perindopril is a specific competitive angiotensin I converting enzyme inhibitor. The administration of perindopril to patients with essential hypertension results in a reduction in supine and standing blood pressure without any significant effect on heart rate. Abrupt withdrawal of perindopril has not been associated with a rebound rise in blood pressure. Single dose studies have demonstrated that peak inhibition of ACE activity and peak reduction in blood pressure occurs 4-6 hours after administration. The durations of these effects are dose related and at the recommended dose range, both effects have been shown to be maintained over a 24-hour period.

In haemodynamic studies carried out in animal models of hypertension, blood pressure reduction after perindopril administration was accompanied by a reduction in peripheral arterial resistance and improved arterial wall compliance. In studies carried out in patients with essential hypertension the reduction in blood pressure was accompanied by a reduction in peripheral resistance with no change, or a small increase in renal blood flow and no change in glomerular filtration rate. An increase in the compliance of large arteries was also observed. When perindopril is administered together with a thiazide-type diuretic, the antihypertensive activity of perindopril may be potentiated in some patients, and this effect is evident after four weeks of treatment. Perindopril, like other ACE inhibitors, may compensate for thiazide-induced hypokalaemia.

In one study of 48 patients where low-dose perindopril equivalent to perindopril arginine 2.5 mg was compared with correspondingly low doses of enalapril (2.5 mg) or captopril (6.25 mg) in patients with congestive heart failure, significantly different blood pressure responses were noted. Blood pressure fell significantly with captopril and enalapril following the first dose. However, whilst perindopril inhibited plasma ACE comparably with enalapril, the blood pressure changes were insignificant and similar to placebo for up to 10 hours of regular observation. The possibility of late hypotensive response cannot be ruled out with perindopril.

*Related to Amlodipine*

**Hypertension**

Following administration of therapeutic doses to patients with hypertension, amlodipine produces vasodilation resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing.

With chronic once daily oral administration, antihypertensive effectiveness is maintained for at least 24 hours. Plasma concentrations correlate with effect in both young and elderly patients.

Amlodipine has shown no harmful effect on lipid levels and is suitable for use in patients with asthma, diabetes and gout.

As with other calcium channel blockers, haemodynamic measurements of cardiac function at rest and during exercise (or pacing) in patients with normal ventricular function treated with amlodipine have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or on left ventricular end diastolic pressure or volume. In haemodynamic studies, amlodipine has not been associated with a negative inotropic effect when administered in the therapeutic dose range to intact animals and man, even when co-administered with beta-blockers to man. Similar findings, however, have been observed in normal or well-compensated patients with heart failure with agents possessing significant negative inotropic effects.

In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow without change in filtration fraction or proteinuria.
CLINICAL TRIALS
Clinical trials using perindopril arginine and amlodipine (as besylate) combination tablets consist of three bioequivalence studies and a pharmacokinetic interaction study (see PHARMACOLOGY, Pharmacokinetics).

No other clinical trials have been conducted with perindopril arginine and amlodipine (as besylate) combination tablets, including trials to assess its long-term effects on cardiovascular morbidity or mortality. However the effects of the individual components of perindopril arginine and amlodipine (as besylate) combination tablets have been assessed in clinical trials as detailed below. The combined use of perindopril and amlodipine has been studied in hypertensive patients with additional cardiovascular risk factors in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA).

Related to Perindopril
Stable Coronary Artery Disease
The effects of perindopril were compared to placebo in patients with stable coronary artery disease with no clinical signs of heart failure. The EUROPA (EUropean trial on Reduction Of cardiac events with perindopril in stable coronary Artery disease) study was a multicentre, international, randomised, double blind, placebo-controlled clinical trial lasting 4 years. 12218 patients aged over 18 were randomised: 6110 patients to high dose perindopril, equivalent to perindopril arginine 10 mg and 6108 patients to placebo.

The primary endpoint was the composite of cardiovascular mortality, non-fatal myocardial infarction, and/or cardiac arrest with successful resuscitation.

The trial population had evidence of coronary artery disease documented by previous myocardial infarction at least 3 months before screening, coronary revascularisation at least 6 months before screening, angiographic evidence of stenosis (at least 70% narrowing of one or more major coronary arteries), or positive stress test in men with a history of chest pain.

Study medication was added to conventional therapy, including medication used for the management of hyperlipidaemia, hypertension and diabetes mellitus. Patients randomised to perindopril were initiated on doses of perindopril equivalent to perindopril arginine 2.5 mg or perindopril arginine 5 mg for 2 weeks, and then titrated up to a dose of perindopril equivalent to perindopril arginine 10 mg during the 2 following weeks. A dose of perindopril arginine 10 mg was then maintained for the whole duration of the study. If this dose was not well tolerated, it could be reduced to a dose of perindopril arginine 5 mg once daily.

Most of the patients also received platelet inhibitors, lipid-lowering agents and beta-blockers. At the end of the study, the proportions of patients on these concomitant medications were 91%, 69% and 63% respectively.

The reduction in the primary composite endpoint was mainly due to a reduction in the number of non-fatal myocardial infarctions. There was no significant reduction in the rate of cardiovascular mortality or total mortality in patients taking perindopril compared to those taking placebo.

After a mean follow-up of 4.2 years, treatment with a dose of perindopril equivalent to perindopril arginine 10 mg once daily resulted in a significant relative risk reduction of 20% (95% CI: 9-29) in the primary combined endpoint: 488 patients (8.0%) reported events in the perindopril group compared to 603 patients (9.9%) in the placebo group (p=0.0003). Improvements in the primary composite endpoint achieved statistical significance after 3 years of continuous treatment on perindopril.
Related to Amlodipine

Electrophysiologic Effects
Amlodipine does not change sinoatrial nodal function or atrioventricular conduction in intact animals or man. In patients with chronic stable angina, intravenous administration of 10 mg of amlodipine and a further 10 mg of amlodipine after a 30 minute interval produced peripheral vasodilation and afterload reduction, but did not significantly alter A-H and H-V conduction and sinus node recovery time after pacing. Similar results were obtained in patients receiving amlodipine and concomitant beta-blockers. In clinical studies in which amlodipine was administered in combination with beta-blockers to patients with either hypertension or angina, no adverse events on electrocardiographic parameters were observed. In clinical trials with angina patients alone, amlodipine therapy did not alter electrocardiographic intervals or produce higher degrees of AV block.

Effects in Hypertension
In patients with hypertension once daily dosing provides clinically significant reductions of blood pressure in both the supine and standing positions throughout the 24 hour interval post dose. Due to the slow onset of action, acute hypotension is not a feature of amlodipine administration. The blood pressure effect is maintained over the 24 hour dosing interval, with little difference in peak and trough effect. Tolerance has not been demonstrated in patients studied for up to 1 year. Effects on diastolic pressure were similar in young and older patients. The effect on systolic pressure was greater in older patients, perhaps because of greater baseline systolic pressure.

Effects in Chronic Stable Angina
In patients with angina, once daily administration of amlodipine increases total exercise time to angina onset and total work time to 1 mm ST segment depression and decreases both angina attack frequency and nitroglycerine tablet consumption. The sustained efficacy of amlodipine in angina patients has been demonstrated over long-term dosing. In patients with angina there were no clinically significant reductions in blood pressure (4/1 mmHg) or changes in heart rate (+0.3 bpm).

Studies in Patients with Congestive Heart Failure
Amlodipine (5-10 mg per day) has been studied in a placebo-controlled trial of 1153 patients with NYHA Class III or IV heart failure on stable doses of ACE inhibitor, digoxin and diuretics. Follow-up was at least 6 months, with a mean of about 14 months. There was no effect on the primary endpoint of the study of all-cause mortality and cardiac morbidity (as defined by life-threatening arrhythmia, acute myocardial infarction, or hospitalisation for worsened heart failure), or on NYHA classification or symptoms of heart failure.

Amlodipine has been compared to placebo in four 8-12 week studies of patients with NYHA class II/III heart failure, involving a total of 697 patients. In these studies, efficacy in regard to the primary and secondary endpoints was not demonstrated and there was no evidence of worsened heart failure based on measures of exercise tolerance, NYHA classification, symptoms, or LVEF (see PRECAUTIONS).

INDICATIONS
Perindopril arginine and amlodipine combination tablets are indicated as substitution therapy for the treatment of hypertension and/or stable coronary heart disease in patients already controlled with separate doses of perindopril and amlodipine, given concurrently at the same dose level. Treatment should not be initiated with this combination.

CONTRAINDICATIONS
Perindopril arginine and amlodipine combination tablets are contraindicated:

- in patients with a history of previous hypersensitivity to either of the active ingredients; perindopril or amlodipine, ACE-inhibitors, dihydropyridines or excipient ingredients present in perindopril arginine and amlodipine combination tablets.
- during pregnancy and for lactating women
All contraindications related to the individual components, as listed below, should also apply to the fixed combination of Perindopril/Amlodipine Tablets.

Related to Perindopril Component
- in patients with bilateral or unilateral renal artery stenosis
- in patients with a history of hereditary and/or idiopathic angio-oedema or angio-oedema associated with previous ACE-inhibitor treatment, and
- in patients haemodialysed using high-flux polyacrylonitrile ("AN69") membranes who are highly likely to experience anaphylactoid reactions if they are treated with ACE inhibitors. This combination should therefore be avoided, either by use of alternative antihypertensive drugs or alternative membranes (e.g. cuprophane or polysulphone PSF)

Related to Amlodipine Component
- severe hypotension
- shock, including cardiogenic shock
- obstruction of the outflow-tract of the left ventricle (e.g. high grade aortic stenosis)
- unstable angina pectoris (excluding Prinzmetal's angina)
- heart failure after acute myocardial infarction

PRECAUTIONS
Related to Perindopril Component

Hyperkalaemia
Since ACE inhibitors reduce angiotensin II formation resulting in decreased production of aldosterone, increases in serum potassium have been observed in some patients treated with ACE inhibitors including perindopril. Risk factors for the development of hyperkalaemia include those with renal insufficiency, worsening of renal function, age (>70 years), diabetes mellitus, intercurrent events, in particular dehydration, acute cardiac decompensation, metabolic acidosis and concomitant use of potassium-sparing diuretics (e.g. spironolactone, eplerenone, triamterene, or amiloride), potassium supplements or potassium-containing salt substitutes; or those patients taking other drugs associated with increases in serum potassium (e.g. heparin). If concomitant use of the above-mentioned agents is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium (see INTERACTIONS WITH OTHER MEDICINES). In some patients hyponatraemia may co-exist with hyperkalaemia. Hyperkalaemia can cause serious, sometimes fatal, arrhythmias. It is recommended that serum electrolytes (including sodium potassium and urea) should be measured from time to time when ACE inhibitors are given, especially when diuretics are also prescribed.

Diabetic Patients
In diabetic patients treated with oral antidiabetic agents or insulin, glycaemic control should be closely monitored during the first month of treatment with an ACE inhibitor (see INTERACTIONS WITH OTHER MEDICINES).

Lithium
The combination of lithium and perindopril is generally not recommended (see INTERACTIONS WITH OTHER MEDICINES).

Potassium Sparing Drugs, Potassium Supplements or Potassium-Containing Salt Substitutes
The combination of perindopril and potassium sparing drugs, potassium supplements or potassium-containing salt substitutes is generally not recommended (see INTERACTIONS WITH OTHER MEDICINES).

Angio-Oedema
Patients with a history of angio-oedema unrelated to ACE inhibitor therapy may be at increased risk of angio-oedema while receiving an ACE inhibitor.
Life-threatening angio-oedema has been reported with most ACE inhibitors. The overall incidence is approximately 0.1% - 0.2%. The aetiology is thought to be non-immunogenic and may be related to accentuated bradykinin activity. Usually the angio-oedema is non-pitting oedema of the skin mucous membrane and subcutaneous tissue.

Angio-oedema of the face, extremities, lips, tongue, mucous membranes, glottis and/or larynx has been reported in patients with ACE inhibitors and has been reported uncommonly with perindopril (see ADVERSE EFFECTS). This may occur at any time during therapy. In such cases treatment should be promptly discontinued and the patient carefully observed until the swelling disappears.

Where such cases have been described with other ACE inhibitors and swelling has been confined to the face and lips, the condition has generally resolved without treatment although antihistamines have been useful in relieving symptoms. Angio-oedema associated with laryngeal oedema may be fatal or near fatal. In most cases symptoms occurred during the first week of treatment and the incidence appears to be similar in both sexes or those with heart failure or hypertension.

Where there is involvement of the tongue, glottis or larynx likely to cause airway obstruction, appropriate therapy (e.g. adrenaline and oxygen) should be given promptly. Treatment of progressive angio-oedema should be aggressive and failing a rapid response to medical therapy, mechanical methods to secure an airway should be undertaken before massive oedema complicates oral or nasal intubation.

Patients who respond to medical treatment should be observed carefully for a possible rebound phenomenon.

The onset of angio-oedema associated with use of ACE inhibitors may be delayed for weeks or months.

Patients may have multiple episodes of angio-oedema with long symptom-free intervals.

Angio-oedema may occur with or without urticaria.

Intestinal angio-oedema has been reported rarely in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior facial angio-oedema and C-1 esterase levels were normal. The angio-oedema was diagnosed by procedures including abdominal CT scan, or ultrasound or at surgery and symptoms resolved after stopping the ACE inhibitor. Intestinal angio-oedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain.

There are reports when changing a patient to another ACE inhibitor was followed by recurrence of angio-oedema and others where it was not. Because of the potential severity of this rare event, another ACE inhibitor should not be used in patients with a history of angio-oedema, to a drug of this class (see CONTRAINDICATIONS). Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor.

Anaphylactoid Reactions During Low-Density Lipoproteins (LDL) Apheresis

Rarely, patients receiving ACE inhibitors during low-density lipoprotein (LDL) apheresis with dextran sulphate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE inhibitor therapy prior to each apheresis.

Anaphylactic Reactions During Desensitisation

Patients receiving ACE inhibitors during desensitisation treatment (e.g. hymenoptera venom) have experienced anaphylactoid reactions. In the same patients, these reactions have been avoided when the ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge.

Hypotension

Hypotension has been reported in patients commencing treatment with ACE inhibitors. Excessive hypotension is rarely seen in uncomplicated hypertension but is a potential consequence of perindopril use in severely salt/volume-depleted patients with impaired renal function, those treated vigorously with diuretics, after severe diarrhoea or patients on dialysis. Administration of a dose of perindopril
equivalent to perindopril arginine 2.5 mg to patients with mild-moderate heart failure was not associated with any significant reduction in blood pressure.

In patients with severe congestive heart failure, with or without associated renal impairment, excessive hypotension has been observed. This may be associated with syncope, neurological deficits, oliguria and/or progressive increase in blood nitrogen, and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started at low doses under very close supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dosage is increased, or diuretic therapy is commenced or increased.

Patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in myocardial infarction or cerebrovascular accident should be closely followed for the first two weeks of treatment and whenever the dose of perindopril and/or diuretic is increased.

If hypotension occurs the patient should be placed in a supine position and if necessary infused with normal saline. A transient hypotensive response is not a contraindication to further doses, which can usually be given without difficulty when blood pressure has increased following volume expansion.

**Impaired Renal Function**

As a consequence of inhibiting the renin-angiotensin-aldosterone system (RAAS), changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on RAAS activity, treatment with ACE inhibitors may be associated with oliguria and/or progressive increase in blood nitrogen, and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea, nitrogen and serum creatinine were observed in 20% of patients. These increases are usually reversible upon discontinuation of ACE inhibitor treatment. ACE inhibitors should be avoided in patients with known or suspected renal artery stenosis. When an ACE inhibitor is given to a patient with stenosis of the renal artery supplying a solitary kidney, or bilateral renal artery stenosis, acute renal insufficiency may occur. ACE inhibition may also cause a decrease in renal function in patients with stenosis of the artery supplying a transplanted kidney. It is believed that renal artery stenosis reduces the pressure in the afferent glomerular arteriole, and transglomerular hydrostatic pressure is then maintained by angiotensin II-induced constriction of the efferent arteriole. When an ACE inhibitor is given, the efferent arteriole relaxes, glomerular filtration pressure falls, and renal failure may result. The thrombotic occlusion of a stenosed renal artery can be precipitated by ACE inhibitors.

If renovascular hypertension is also present there is an increased risk of severe hypotension and renal insufficiency. In these patients, treatment should be started under close medical supervision with low doses and careful dose titration. Since treatment with diuretics may be a contributory factor to the above, they should be discontinued and renal function should be monitored during the first weeks of perindopril therapy.

Some hypertensive patients with no apparent pre-existing renovascular disease have developed increases in blood urea, nitrogen and serum creatinine, which are usually minor and transient. This is more likely to occur in patients with pre-existing renal impairment or in those on diuretics. Dosage reduction of the ACE inhibitor and/or discontinuation of the diuretic may be required. Evaluation of the hypertensive patient should always include assessment of renal function (see DOSAGE AND ADMINISTRATION). Routine monitoring of potassium and creatinine are part of normal medical practice for these patients (see ADVERSE EFFECTS). If deterioration in renal function has occurred after treatment with one ACE inhibitor, then it is likely to be precipitated by another and in these patients usage of another class of antihypertensive agent would be preferable. Patients with unilateral renal artery disease present a special problem as deterioration of function may not be apparent from measurement of blood urea and serum creatinine.

Some ACE inhibitors have been associated with the occurrence of proteinuria (up to 0.7%) and/or decline in renal function in patients with one or more of the following characteristics: old age, pre-existing renal disease, concomitant treatment with potassium-sparing diuretics or high doses of other diuretics, limited cardiac reserve, or treatment with a non-steroidal anti-inflammatory drug.
Perindopril is dialysable with a clearance of 70mL/min.

Kidney Transplantation

There is no experience regarding the administration of perindopril arginine and amlodipine (as besylate) combination tablets in patients with a recent kidney transplantation.

Hepatic Failure

Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up (see ADVERSE EFFECTS).

Impaired Hepatic Function

Biotransformation of perindopril to perindoprilat mainly occurs in the liver. Studies in patients with impaired hepatic function have shown that kinetic parameters of perindopril were not modified by hepatic failure. With the exception of bioavailability, which was increased, kinetic parameters of perindoprilat (including $T_{\text{max}}$) were also unchanged. The increase in bioavailability could be due to inhibition of the formation of perindopril metabolites other than perindoprilat (see PHARMACOLOGY, Pharmacokinetics). The administration of perindopril leads to the formation of a glucurononconjugate derivative of perindoprilat by a hepatic first-pass effect. The kinetic parameters of perindoprilat glucuronide are not modified by hepatic failure. The small changes in the kinetics of perindoprilat do not justify the need to change the usual dosage in most patients with hepatic failure.

Ethnicity

ACE inhibitors cause a higher rate of angioedema in patients of indigenous African origin than in patients of other racial origin. As with other ACE inhibitors, perindopril may be less effective in lowering blood pressure in people of indigenous African origin than in people of other racial origin, possibly because of a higher prevalence of low-renin states in this population. It is unknown if the same observations have been made in patients of indigenous Australian origin.

Cough

A persistent dry (non-productive) irritating cough has been reported with most of the ACE inhibitors. The frequency of reports has been increasing since cough was first recognised as a class-effect of ACE inhibitor therapy with the incidence of cough varying between 2-15% depending upon the drug, dosage and duration of use.

The cough is often worse when lying down or at night, and has been reported more frequently in women (who account for 2/3 of the reported cases). Patients who cough may have increased bronchial reactivity compared with those who do not. The observed higher frequency of this side effect in non-smokers may be due to a higher level of tolerance of smokers to cough.

The cough is most likely due to stimulation of the pulmonary cough reflex by kinins (bradykinin) and/or prostaglandins, which accumulate because of ACE inhibition. Once a patient has developed intolerable cough, an attempt may be made to switch the patient to another ACE inhibitor; the reaction may recur but this is not invariably the case. A change to another class of drugs may be required in severe cases.

Proteinuria

Perindopril treatment has occasionally been associated with mild or transient proteinuria (<1gram/per 24 hours). However in the majority of patients with pre-existing proteinuria treated with perindopril, proteinuria disappeared or remained stable. ACE inhibitors have a real potential to delay the progression of nephropathy in diabetic as well as hypertensive patients.

Neutropenia / Agranulocytosis / Thrombocytopenia / Anaemia

Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. Perindopril should be used with extreme caution in patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of
these complicating factors, especially if there is pre-existing impaired renal function. Some of these patients developed serious infections, which in a few instances did not respond to intensive antibiotic therapy. If perindopril is used in such patients, periodic monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection (e.g. sore throat, fever).

**Dermatological Reactions**

Dermatological reactions characterised by maculo-papular pruritic rashes and sometimes photosensitivity has been reported with another ACE inhibitor. Rare and sometimes severe skin reactions (lichenoid eruptions, psoriasis, pemphigus like rash, rosacea, Stevens-Johnson syndrome etc). A causal relationship is difficult to assess.

Patients who develop a cutaneous reaction with one ACE inhibitor might not when switched to another drug of the same class, but there are reports of cross-reactivity.

**Taste Disturbances (Dysgeusia)**

Taste disturbances were reported to be common (prevalence up to 12.5%) with high doses of one ACE inhibitor. The actual incidence of taste disturbance is probably low (<0.5%) but data are scarce and difficult to interpret.

Taste disturbances with ACE inhibitors have been described as suppression of taste or a metallic sensation in the mouth. Any dysgeusia usually occurs in the first weeks of treatment and may disappear in most cases within 1-3 months.

**Agents Causing Renin Release**

The effects of perindopril may be enhanced by concomitant administration of antihypertensive agents which cause renin release.

**Dual Blockade of the Renin-Angiotensin-Aldosterone System**

As a consequence of inhibiting the renin-angiotensin-aldosterone system, hypotension, syncope, hyperkalaemia, and changes in renal function (including acute renal failure) have been reported in susceptible individuals, especially if combining medicinal products that affect this system. Dual blockade of the renin-angiotensin-aldosterone system (e.g. by adding an angiotensin II receptor antagonist to an ACE-inhibitor) is therefore not recommended in patients with already controlled blood pressure and should be limited to individually defined cases with close monitoring of renal function.

**Surgery and Anaesthesia**

In patients undergoing major surgery or who require anaesthesia, hypotension due to anaesthetic agents may be greater in patients receiving ACE inhibitors because of interference with compensatory mechanisms associated with the renin-angiotensin system. The treatment should be discontinued one day prior to the surgery. If perioperative hypotension occurs, volume expansion would be required.

**Aortic or Mitral Valve Stenosis / Hypertrophic Cardiomyopathy**

There has been some concern on theoretical grounds that patients with mitral valve stenosis and obstruction in the outflow of the left ventricle such as aortic stenosis or with hypertrophic cardiomyopathy might be at particular risk of decreased coronary perfusion when treated with vasodilators, including ACE inhibitors. Vasodilators may tend to drop diastolic pressure, and hence coronary perfusion pressure, without producing the concomitant reduction in myocardial oxygen demand that normally accompanies vasodilatation. The true clinical importance of this concern is uncertain.

**Diabetic Patients**

In diabetic patients treated with oral antidiabetic agents or insulin, glycaemic control should be closely monitored during the first month of treatment with any ACE inhibitor.

**Stable Coronary Artery Disease**
If an episode of unstable angina pectoris, regardless of severity, occurs during the first month of perindopril treatment, a careful appraisal of the benefits/risks of continuing treatment should be performed.

**Related to Amlodipine Component**

**Increased Angina**

Rarely patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration and/or severity of angina on starting calcium channel blocker therapy or at the time of dosage increase. The mechanism of this effect has not been elucidated.

**Outflow Obstruction (Aortic Stenosis)**

Amlodipine should be used with caution in the presence of a fixed left ventricular outflow obstruction (aortic stenosis).

**Use in Patients with Congestive Heart Failure**

Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure.

In a long-term, placebo controlled study of amlodipine in patients with NYHA III and IV heart failure of non-ischaemic aetiology, amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo (see CLINICAL TRIALS).

**Use in Patients with Impaired Hepatic Function**

There are no adequate studies in patients with liver dysfunction and dosage recommendations have not been established. In a small number of patients with mild to moderate hepatic impairment given single doses of 5mg, amlodipine half-life has been prolonged. Worsening of liver function test values may occur. Amlodipine should, therefore, be administered with caution in these patients and careful monitoring should be performed. A lower starting dose of amlodipine may be required (see DOSAGE AND ADMINISTRATION).

**Use in Impaired Renal Function**

Amlodipine is extensively metabolised to inactive metabolites with 10% excreted as unchanged drug in the urine. Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment. Amlodipine may be used in such patients at normal doses.

Amlodipine is not dialysable.

**Peripheral Oedema**

Mild to moderate peripheral oedema was the most common adverse event in clinical trials. The incidence of peripheral oedema was dose-dependent and ranged in frequency from 3.0 to 10.8% in 5 to 10 mg dose range. Care should be taken to differentiate this peripheral oedema from the effects of increasing left ventricular dysfunction.

**Effects on Fertility**

No animal studies with perindopril arginine and amlodipine (as besylate) combination tablets have been performed.

**Related to Perindopril Component**

The effects of perindopril arginine on fertility have not been investigated. Studies in rats showed no impairment of male or female fertility at oral perindopril erbumine doses up to 10 mg/kg/day.

**Related to Amlodipine Component**

In animal studies, amlodipine did not affect fertility in rats at oral doses up to 18 mg/kg (base).

**Use in Pregnancy (Category D)**
No animal studies with perindopril arginine and amlodipine (as besylate) combination tablets have been performed.

Perindopril arginine and amlodipine combination tablets should not be initiated during pregnancy. Patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with perindopril and amlodipine combination tablets should be stopped immediately, and, if appropriate, alternative therapy should be started.

**Related to Perindopril Component**
The use of ACE inhibitors is contra-indicated during pregnancy (see **CONTRAINDICATIONS**).

As with all ACE inhibitors, perindopril should not be taken during pregnancy. Pregnancy should be excluded before starting treatment with perindopril and avoided during the treatment. Unless continued ACE inhibitor therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. If a patient intends to become pregnant, treatment with ACE inhibitors must be discontinued and replaced by another form of treatment. If a patient becomes pregnant while on ACE inhibitors, she must immediately inform her doctor to discuss a change in medication and further management.

There are no adequate and well-controlled studies of ACE inhibitors in pregnant women, but foetotoxicity is well documented in animal models. Data, however, show that ACE inhibitors cross the human placenta. Post marketing experience with all ACE inhibitors suggests that exposure in utero may be associated with hypotension and decreased renal perfusion in the foetus. ACE inhibitors have also been associated with foetal death in utero.

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded.

A historical cohort study in over 29,000 infants born to non-diabetic mothers has shown 2.7 times higher risk for congenital malformations in infants exposed to ACE inhibitors during the first trimester compared to no exposure. The risk ratios for cardiovascular and central nervous system malformations were 3.7 times (95% confidence interval 1.89 to 7.3) and 4.4 times (95% confidence interval 1.37 to 14.02) respectively, compared to no exposure.

When ACE inhibitors have been used during the second and third trimesters of pregnancy, there have been reports of foetal and neonatal toxicity, hypotension, hyperkalaemia, renal failure, skull hypoplasia, oligohydramnios and death.

Oligohydramnios has been reported, presumably resulting from decreased foetal renal function; oligohydramnios has been associated with foetal limb contractures, craniofacial deformities, hypoplastic lung development and intra-uterine growth retardation. Prematurity and patent ductus arteriosus have been reported, however it is not clear whether these events were due to ACE inhibitor exposure or to the mother's underlying disease.

Infants exposed in utero to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalaemia. Should exposure to ACE inhibitor have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. If such complications arise, appropriate medical treatment should be initiated to support blood pressure and renal perfusion. While small amounts of perindopril are found in the breast milk of animals, there is no human data.

**Related to Amlodipine Component**
Calcium channel blockers carry the potential to produce foetal hypoxia associated with maternal hypotension. Accordingly they should not be used in pregnant women unless the potential benefit outweighs the risk to the foetus.

The safety of amlodipine in human pregnancy or lactation has not been established. Amlodipine (10mg/kg as besylate salt, 7mg/kg base), administered orally to rats at or near parturition induced a
prolongation of gestation time, an increase in the number of stillbirths and a decreased postnatal survival.

Use in Lactation
No animal studies with perindopril arginine and amlodipine (as besylate) combination tablets have been performed.

Related to Perindopril Component
Alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or pre-term infant.

Animal studies have shown that perindopril and its metabolites are excreted in milk during lactation, but there are no human data. It is therefore recommended that perindopril should not be given to lactating women as the possible effect on the newborn is unknown.

Related to Amlodipine Component
It is not known whether amlodipine is excreted in human milk. In the absence of this information, breast-feeding should be discontinued during treatment with amlodipine.

Paediatric Use
Use of perindopril arginine and amlodipine (as besylate) combination tablets in children is not recommended as no data establishing safety or effectiveness in children are available.

Use in the Elderly

Related to Perindopril Component
Care should be taken when prescribing perindopril to elderly patients.

In a study of 91 elderly patients with a mean age of 71.9 years, a 6% increase in serum potassium occurred in the first month of treatment and subsequently remained stable. There was no change in the group in blood urea, creatinine or creatinine clearance.

Particular care should be taken in elderly patients with congestive heart failure who have renal and/or hepatic insufficiency.

Related to Amlodipine Component
In elderly patients (>65 years) clearance of amlodipine is decreased with a resulting increase in AUC. In clinical trials the incidence of adverse reactions in elderly patients was approximately 6% higher than that of younger population (<65 years). Adverse reactions include oedema, muscle cramps and dizziness. Amlodipine should be used cautiously in elderly patients.

Genotoxicity
No animal studies with perindopril arginine and amlodipine (as besylate) combination tablets have been performed.

Related to Perindopril Component
At least one ACE inhibitor has caused an increase in the incidence of oxyphilic renal tubular cells and oncocytomas in rats. The potential of ACE inhibitors to cause this effect in man is unknown.

Moreover, the progression of oxyphilic cells to oncocytomas is rare in humans and when it does occur, it is considered to be benign. Results from a broad set of assays for gene mutation and chromosomal damage with perindopril arginine suggest no genotoxic potential at clinical doses.

Related to Amlodipine Component
In animal studies, amlodipine had no teratogenic effects in rats (18mg/kg) or rabbits (10mg/kg). Results from a broad set of assays for gene mutation and chromosomal damage with perindopril arginine suggest no genotoxic potential at clinical doses.

Carcinogenicity
No animal studies with perindopril arginine and amlodipine (as besylate) combination tablets have been performed.

Related to Perindopril Component
Carcinogenicity studies have not been conducted with perindopril arginine. No evidence of carcinogenic activity was observed in mice and rats when perindopril erbumine was administered via drinking water at levels up to 7.5 mg/kg/day for 2 years.

Related to Amlodipine Component
The carcinogenic potential of amlodipine has not been fully elucidated. Amlodipine did not induce any tumours when tested in rats at oral doses up to 2.5 mg/kg. This dose gave rise to plasma levels that are similar to those achieved clinically.

Effects on Laboratory Tests
Reported with Perindopril Component
Elevation of liver enzymes and serum bilirubin have been reported rarely.

Increases in blood urea, serum creatinine and hyperkalaemia have also been reported.

Reported with Amlodipine Component
Amlodipine therapy has not been associated with clinically significant changes in routine laboratory tests. Hepatic enzymes elevations: ALT, AST (mostly consistent with cholestasis) have been reported very rarely.

Effects on the Ability to Drive or Operate Machinery
No studies on the effects of perindopril arginine and amlodipine (as besylate) combination tablets on the ability to drive and use machines have been performed. The antihypertensive effect in individual cases may be symptomatic. Treatment with any blood pressure lowering agent may, therefore, affect the ability to drive, cross the road safely or operate machinery, especially at the start of treatment or when changing over from other preparations, or during concomitant use of alcohol. Amlodipine can have minor or moderate influence on the ability to drive and use machinery. If patients suffer from dizziness, headache, fatigue, weariness or nausea, the ability to react may be impaired. Caution is recommended particularly at initiation of treatment with perindopril arginine and amlodipine (as besylate) combination tablets.

INTERACTIONS WITH OTHER MEDICINES
Related to Perindopril Component
Concomitant Use Not Recommended
Potassium Sparing Diuretics, Potassium Supplements or Potassium-Containing Salt Substitutes:
The ACE inhibitor class can attenuate potassium loss caused by thiazide diuretics and increase serum potassium when used alone. Although serum potassium usually remains within normal limits, hyperkalaemia may occur in some patients treated with perindopril, the concomitant use of an ACE inhibitor with a potassium-sparing diuretic (e.g. spironolactone, triamterene, or amiloride), immunosuppressant (e.g. cyclosporin), angiotensin receptor blocker, potassium supplements, or potassium-containing salt substitute can increase the risk of hyperkalaemia, therefore the combination of perindopril with the above mentioned drugs is not recommended (see PRECAUTIONS). If co-administration is indicated they should be used with caution and the patient's serum potassium monitored frequently.

Lithium:
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Concomitant use of thiazide diuretics may increase the risk of lithium toxicity and enhance the already increased risk of lithium toxicity with ACE inhibitors. Use of perindopril with lithium is not recommended, but if the combination is necessary, careful monitoring of serum lithium levels should be performed (see PRECAUTIONS).

Concomitant Use which Requires Special Care

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) Including Aspirin ≥ 3 g/day:

Drugs with prostaglandin synthetase inhibitor properties (e.g. indomethacin) or non-steroidal anti-inflammatory drug (i.e. acetylsalicylic acid at anti-inflammatory dosage regimens, non-selective NSAIDs or COX-2 inhibitor), may diminish the antihypertensive efficacy of concomitantly administered ACE inhibitors. However, clinical studies have not demonstrated any interaction between perindopril or indomethacin or other non-steroidal anti-inflammatory drugs. The administration of a non-steroidal anti-inflammatory drug may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

ACE Inhibitors, Anti-Inflammatory Drugs and Thiazide Diuretics:

The use of an ACE inhibiting drug (ACE-inhibitor or angiotensin receptor antagonist), an anti-inflammatory drug (NSAID or COX-2 inhibitor) and a thiazide diuretic at the same time increases the risk of renal impairment. This includes use in fixed-combination products containing more than one class of drug. Combined use of these medications should be accompanied by increased monitoring of serum creatinine, particularly at the institution of the combination. The combination of drugs from these three classes should be used with caution particularly in elderly patients or those with pre-existing renal impairment.

Antidiabetic Agents (Insulin, Hypoglycaemic Sulphonamides):

Reported with captopril and enalapril.

The use of ACE inhibitors may increase the hypoglycaemic effect in diabetics receiving treatment with insulin or with hypoglycaemic sulphonylureas. The onset of hypoglycaemic episodes is very rare (improvement in glucose tolerance with a resulting reduction in insulin requirements) and appeared to be more likely to occur during the first weeks of combined treatment and in patients with renal impairment.

Concomitant Use to be Taken into Consideration

Diuretics:

When a diuretic is added to the therapy of a patient receiving an ACE inhibitor, the antihypertensive effect is usually additive. Patients receiving diuretics, especially those in whom diuretic therapy was recently instituted or in those with intravascular volume depletion, may sometimes experience an excessive reduction of blood pressure after initiation of therapy with an ACE inhibitor. The possibility of hypotensive effects may be minimised by discontinuation of the diuretic and/or ensuring adequate hydration and salt intake prior to commencing ACE inhibitor therapy. The starting dose of the ACE-inhibitor should be reduced and the patient closely observed for several hours following the initial dose of the ACE inhibitor and until the blood pressure has stabilised.

Antihypertensive Agents and Vasodilators:

Concomitant use of these agents may increase the hypotensive effects of perindopril. Concomitant use with nitroglycerin and other nitrates, or other vasodilators, may further reduce blood pressure.

Gold:

Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy including perindopril.
Tetracycline and Other Drugs that Interact with Magnesium:
The simultaneous administration of tetracycline with an ACE inhibitor may significantly reduce the absorption of tetracycline, possibly due to the magnesium content in the ACE inhibitor tablets. This interaction should be considered if co-prescribing an ACE inhibitor and tetracycline or other drugs that interact with magnesium.

Agents Affecting Sympathetic Activity:
As the sympathetic nervous system plays an important part in physiological blood pressure regulation, caution should be exercised with concomitant administration of a drug with sympathetic activity and perindopril. Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

Acetylsalicylic Acid, Thrombolytics, Beta-Blockers, Nitrates:
Perindopril may be used concomitantly with thrombolytics, acetylsalicylic acid (when used as a thrombolytic), beta-blockers and/or nitrates.

Tricyclic Antidepressants / Antipsychotics / Anaesthetics:
Concomitant use of certain anaesthetic medicinal products, tricyclic antidepressants and antipsychotics with ACE inhibitors may result in further reduction of blood pressure (see PRECAUTIONS).

Related to Amlodipine Component
Amlodipine has been safely administered with thiazide diuretics, beta-blockers, angiotensin converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerine, non-steroidal anti-inflammatory drugs, antibiotics and oral hypoglycaemic drugs.

Concomitant Use Not Recommended
Dantrolene (Infusion):
In animals, lethal ventricular fibrillations are observed after administration of verapamil, and intravenous dantrolene. By extrapolation, the combination of calcium channel blockers such as amlodipine, and dantrolene should be avoided.

Concomitant Use which Requires Special Care
CYP3A4 Inducers (Rifampicin, Hypericum perforatum (St John’s Wort), Anticonvulsant Agents i.e Carbamazepine, Phenobarbitone, Phenytoin, Primidone):
There are no data available regarding the effect of CYP3A4 inducers on amlodipine. Co-administration may lead to reduced plasma concentration of amlodipine due to an increase of the hepatic metabolism of amlodipine by these inducers. Caution should be exercised with this combination and the dose of amlodipine should be adjusted if necessary.

CYP3A4 Inhibitors (Erythromycin in Young Patients or Diltiazem in Elderly Patients)
Co-administration with strong or moderate CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, ritonavir) may significantly increase the plasma concentration of amlodipine and consequently its adverse effects. Caution should be exercised when combining amlodipine with strong or moderate CYP3A4 inhibitors and the dose of amlodipine should be adjusted if necessary.

Baclofen:
Potentiation of antihypertensive effect. Monitoring of blood pressure and renal function, and dose adaptation of the antihypertensive if necessary.

Concomitant Use to be Taken into Consideration
Concomitant use of amlodipine with other medicines with antihypertensive properties may further reduce blood pressure.

Beta-Blockers used in Heart Failure (Bisoprolol, Carvedilol, Metoprolol):
Risk of hypotension, heart weakness in patients with cardiac heart failure, be it latent or uncontrolled (addition of negative inotrope effect). Furthermore, the beta-blocker may minimise the sympathetic reflex in the case of excessive haemodynamic repercussion.
Antihypertensive Agents (such as Beta-Blockers) and Vasodilatators:
Concomitant use of these agents may increase the hypotensive effects of perindopril and amlodipine.

Concomitant use with nitroglycerine and other nitrates or other vasodilatators, may further reduce blood pressure and therefore should be considered with caution.

Corticosteroids:
Reduction in antihypertensive effect (salt and water retention due to corticosteroids).

Alpha-blockers (Prazosin, Tamsulosin, Terazosin):
Increased antihypertensive effect and increased risk of orthostatic hypotension.

Amifostine:
May potentiate the antihypertensive effect of amlodipine.

Tricyclic Antidepressants / Antipsychotics / Anaesthetics:
Increased antihypertensive effect and increased risk of orthostatic hypotension.

Other Concomitant Use
Specific studies conducted with other drugs have shown no influence on amlodipine.

Cimetidine:
Co-administration of amlodipine with cimetidine did not alter the pharmacokinetics of amlodipine.

Sildenafil:
A single 100 mg dose of sildenafil in 16 patients with essential hypertension had no effect on the pharmacokinetic parameters of amlodipine. When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

Aluminium / Magnesium (Antacid):
Co-administration of an aluminium/magnesium antacid with a single dose of amlodipine had no significant effect on the pharmacokinetics of amlodipine.

Grapefruit Juice:
Grapefruit juice is known to inhibit the cytochrome P450 system, thereby affecting the pharmacokinetics of drugs such as calcium channel blockers.

In a study of 20 healthy volunteers, co-administration of 240mL of grapefruit juice with a single oral dose of 10mg amlodipine had no significant effect on the pharmacokinetics of amlodipine.

Specific studies conducted with other drugs have shown that amlodipine has no influence on the pharmacokinetics parameters of those drugs:

Atorvastatin:
Co-administration of multiple doses of 10mg amlodipine with 80mg of atorvastatin resulted in no significant change in the steady-state pharmacokinetics parameters of atorvastatin.

Digoxin:
Co-administration of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers.

Warfarin:
In healthy male volunteers, the co-administration of amlodipine did not significantly alter the effect of warfarin on prothrombin response time. Co-administration of amlodipine with warfarin did not change the warfarin prothrombin response time.
Cyclosporin:
Pharmacokinetic studies with cyclosporin have demonstrated that amlodipine does not significantly alter the pharmacokinetics of cyclosporin. Patients in these studies were not taking corticosteroids.

Alcohol:
Single and multiple 10mg doses of amlodipine had no significant effect on the pharmacokinetics of ethanol.

Related to Perindopril Arginine and Amlodipine Combination Tablets
Concomitant Use which Requires Special Care
Baclofen:
Potentiation of antihypertensive effect. Monitoring of blood pressure and renal function, and dose adaptation of the antihypertensive if necessary.

Concomitant Use to be Taken into Consideration
Antihypertensive Agents (such as Beta-Blockers) and Vasodilators:
Concomitant use of these agents may increase the hypotensive effects of perindopril and amlodipine. Concomitant use with nitroglycerine and other nitrates or other vasodilators, may further reduce blood pressure and therefore should be considered with caution.

Corticosteroids, Tetracosactide:
Reduction in antihypertensive effect (salt and water retention due to corticosteroids).

Alpha-Blockers (Prazosin, Alfuzosin, Doxazosin, Tamsulosin, Terazosin):
Increased antihypertensive effect and increased risk of orthostatic hypotension.

Amifostine:
May potentiate the antihypertensive effect of amlodipine.

Tricyclic Antidepressants / Antipsychotics / Anaesthetics:
Increased antihypertensive effect and increased risk of orthostatic hypotension.

ADVERSE EFFECTS
Three bioequivalence studies using doses equivalent to perindopril arginine and amlodipine (as besylate) combination tablets 5mg/10 mg, 10 mg /10 mg and 10 mg /5 mg, and one pharmacokinetic interaction study between perindopril arginine 10 mg and amlodipine 10 mg revealed no serious adverse effects. All the reported adverse effects were mild or moderate in intensity.

The following undesirable effects have been observed with an amlodipine/perindopril treatment regimen; with perindopril monotherapy; and with amlodipine monotherapy, and ranked under the following frequency:

Very common (>10%); common (>1%, <10%); uncommon (>0.1%, <1%); rare (>0.01%, <0.1%); very rare (>0.001%, <0.01%), not known (cannot be estimated from the available data).

Reported with Amlodipine/Perindopril Treatment Regimen (see PHARMACOLOGY, Pharmacodynamics):
Nervous System Disorders
Very Common: Dizziness
Common: Vertigo

Cardiac Disorders
Common: Chest pain
Uncommon: Bradycardia
Vascular Disorders
Uncommon: Peripheral coldness

Respiratory, Thoracic and Mediastinal Disorders
Very Common: Cough
Common: Dyspnoea

Gastro-intestinal Disorders
Common: Diarrhoea

Skin and Subcutaneous Tissue Disorders
Common: Eczema

Musculoskeletal and Connective Tissue Disorders
Very Common: Joint swelling

Reproductive System and Breast Disorders
Common: Erectile dysfunction

General Disorders and Administration Site Condition
Very Common: Oedema peripheral
Common: Fatigue, lethargy

Reported with Perindopril
Blood and the Lymphatic System Disorders
Very Rare: Leucopenia/neutropenia (see PRECAUTIONS), agranulocytosis or pancytopenia (see PRECAUTIONS), thrombocytopenia (see PRECAUTIONS), haemolytic anaemia in patients with a congenital deficiency of G-6PDH (see PRECAUTIONS), decrease in hemoglobin and haematocrit

Immune System Disorders
Uncommon: Allergic reactions;

Metabolism and Nutrition Disorders
Not Known: Hypoglycaemia (see PRECAUTIONS)

Psychiatric Disorders
Uncommon: Mood changes (including anxiety), sleep disturbances (insomnia, dream abnormality)
Very Rare: Depression, confusion

Nervous System Disorders
Common: Dizziness (especially at the beginning of the treatment), headache (especially at the beginning of the treatment), drowsiness, paresthaesia, vertigo, dysgeusia
Very Rare: Hallucinations

Eye Disorders
Common: Visual disturbances (including diplopia),

Ear and Labyrinth Disorders
Common: Tinnitus

Cardiac Disorders
Common: Palpitations, impaired peripheral circulation
Very rare: Angina pectoris, myocardial infarction, possibly secondary to excessive hypotension in high risk patients (see PRECAUTIONS), arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation)
Vascular Disorders

Common: Flushing, hypotension (and effects related to hypotension)
Very rare: Stroke possibly secondary to excessive hypotension in high-risk patients (see PRECAUTIONS), vasculitis

Respiratory, Thoracic and Mediastinal Disorders

Common: Dyspnoea, epistaxis, discomfort on exertion, cough
Uncommon: Bronchospasm
Very rare: Rhinitis, eosinophilic pneumonia

Gastro-Intestinal Disorders

Common: Abdominal pain, nausea, vomiting, dyspepsia, diarrhoea, constipation
Uncommon: Dry mouth
Very Rare: Pancreatitis

Hepato-Biliary Disorders

Very Rare: Hepatitis either cytolitic or cholestatic (see PRECAUTIONS)

Skin and Subcutaneous Tissue Disorders

Common: Pruritis, rash, exanthema
Uncommon: Angio-edema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx (see PRECAUTIONS), hyperhidrosis, urticaria
Very Rare: Erythema multiform

Musculoskeletal and Connective Tissue Disorders

Common: Muscle cramps

Renal and Urinary Disorders

Uncommon: Renal impairment
Very rare: Acute renal failure

Reproductive System and Breast Disorders

Uncommon: Impotence

General Disorders and Administration Site Conditions

Common: Asthenia
Uncommon: Atypical chest pain

Withdrawals

In total 56 of 1275 patients (4.4%) stopped treatment because of adverse reactions. In a specific study of 632 patients in which 36 (5.7%) patients withdrew because of adverse events, a plausible or probable relationship with perindopril treatment was considered to exist in 19 (3%) cases.

Investigations

Rare: Serum bilirubin elevation, liver enzyme elevation
Not Known: Increases in blood urea and serum creatinine, hyperkalaemia (see PRECAUTIONS)

Reported with Amlodipine

Blood and the Lymphatic System Disorders

Uncommon: Leucopenia, thrombocytopenia
Very Rare: Neutropenia (see PRECAUTIONS)

Immune system Disorders

Uncommon: Allergic reactions
Metabolism and Nutrition Disorders

Uncommon: Thirst, hyperglycaemia, anorexia
Rare: Increased appetite

Psychiatric Disorders

Uncommon: Insomnia, mood changes, sexual dysfunction (male and female), nervousness, depression, dream abnormality, anxiety, depersonalisation, depression
Rare: Apathy, agitation, amnesia, confusion

Nervous System Disorders

Common: Somnolence (particularly at the beginning of treatment), dizziness (particularly at the beginning of the treatment), headache (particularly at the beginning of the treatment)
Uncommon: Tremor, hypoesthesia, paresthesia, vertigo, peripheral neuropathy, dysgeusia, syncope
Rare: Migraine, parosmia
Very Rare: Hypertonia

Eye Disorders

Uncommon: Visual disturbances, conjunctivitis, diplopia, eye pain
Rare: Dry eyes, abnormal visual accommodation

Ear and Labyrinth Disorders

Uncommon: Tinnitus

Cardiac Disorders

Common: Palpitations
Uncommon: Peripheral ischaemia, postural dizziness, postural hypotension, tachycardia
Rare: Myocardial infarction, possibly secondary to excessive hypotension in high risk patients (see PRECAUTIONS), angina pain, cardiac failure, pulse irregularity, extrasystoles, arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation)

Vascular Disorders

Common: Flushing
Uncommon: Hypotension (and effects related to hypotension), vasculitis
Rare: Cold and clammy skin

Respiratory, Thoracic and Mediastinal Disorders

Uncommon: Dyspnoea, rhinitis, epistaxis
Very Rare: Cough

Gastro-intestinal Disorders

Common: Abdominal pain, nausea
Uncommon: Vomiting, dyspepsia, altered bowel habits, dry mouth, taste perversion, anorexia, dysphagia, flatulence, constipation, diarrhoea, gingival hyperplasia, pancreatitis
Rare: Loose stools, gastritis

Hepato-biliary Disorders

Rare: hepatitis, jaundice, hepatic enzyme elevations (mostly consistent with cholestasis)

Skin and Subcutaneous Tissue Disorders

Uncommon: Alopecia, purpura, hyperhidrosis, pruritis, rash, rash erythematous, rash maculopapular, exanthema, skin discoloration, angio-oedema (of the face, extremities, lips, mucous membranes, tongue, glottis and/or larynx – see section PRECAUTIONS)
Rare: Skin dryness, erythema multiform, dermatitis, urticaria
Very Rare: Quincke’s oedema, Stevens-Johnson syndrome, exfoliative dermatitis, photosensitivity
Musculoskeletal and Connective Tissue Disorders

Common: Ankle swelling
Uncommon: Arthralgia, arthropathy, myalgia, muscle cramps, back pain
Rare: Muscle weakness, twitching, ataxia, hypertonnia

Renal and Urinary Disorders

Uncommon: Micturition disorder, nocturia, increased urinary frequency
Rare: Dysuria

Reproductive System and Breast Disorders

Uncommon: Impotence, gynaecomastia

General Disorders and Administration Site Condition

Common: Oedema, peripheral oedema, fatigue
Uncommon: Chest pain, asthenia, pain, malaise, rigors

Investigations

Uncommon: Weight gain, weight decrease

Additional Information Linked to Amlodipine

Exceptional cases of extrapyramidal syndrome have been reported.

DOSAGE AND ADMINISTRATION

Perindopril arginine and amlodipine (as besylate) combination tablet is available in strengths of 5mg/5mg, 5mg/10mg, 10mg/5mg and 10mg/10mg as substitution therapy for patients already controlled with separate doses of perindopril (5 or 10mg) and amlodipine (5 or 10mg), given concurrently at the dose level as indicated in the table below. Treatment should not be initiated with this combination.

Table 1. Dose conversion from perindopril and amlodipine, to Perindopril / Amlodipine Tablets

<table>
<thead>
<tr>
<th>Perindopril and Amlodipine Tablet</th>
<th>Perindopril / Amlodipine Tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perindopril arginine</td>
<td>Perindopril / Amlodipine Tablet</td>
</tr>
<tr>
<td>Arginine or erbumine</td>
<td>5mg</td>
</tr>
<tr>
<td>5 mg</td>
<td>4 mg</td>
</tr>
<tr>
<td>5 mg</td>
<td>4 mg</td>
</tr>
<tr>
<td>10 mg</td>
<td>8 mg</td>
</tr>
<tr>
<td>10 mg</td>
<td>8 mg</td>
</tr>
</tbody>
</table>

Food intake may reduce hepatic biotransformation of perindopril to perindoprilat. Recommended treatment is one tablet per day as a single dose, preferably to be taken in the morning and before a meal.

As perindopril and amlodipine may be used for different clinical indications, dose adjustments should be based on clinical judgment and the individual patient profile.

Adjustments can be made by decreasing or increasing the dose of either perindopril and/or amlodipine using separate perindopril and/or amlodipine products within the recommended dose range until clinical stability is re-established. Consult the Product Information of the individual perindopril and/or amlodipine products being used when adjusting the dose.

In the event that down-titration is required, adjustments using amlodipine 2.5 mg or a dose of perindopril equivalent to perindopril arginine 2.5 mg, as separate products should be considered until clinical stability is re-established.
Patients with Impaired Renal Function and Elderly Patients
Elimination of perindoprilat is decreased in the elderly and in patients with renal failure. Therefore, the usual medical follow-up will include frequent monitoring of creatinine and potassium.

Where down-titration is required to achieve clinical stability in patients with a CrCl <60mL/min, adjustments using amlodipine 2.5 mg or a dose of perindopril equivalent to perindopril arginine 2.5 mg, as separate products should be considered until clinical stability is re-established. Please consult the product information of the individual perindopril or amlodipine products.

Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment.

Amlodipine is not dialysable.

In elderly patients, adjustments using amlodipine and perindopril as separate products should be considered. Small, fragile or elderly individuals should be started on amlodipine 2.5 mg once daily and care should be taken when increasing the dosage of amlodipine. The initial dose of perindopril in the elderly should always be a dose equivalent to perindopril arginine 2.5 mg daily and patients should be monitored closely during the initial stages of treatment.

Patients with Impaired Hepatic Function
Dosage recommendations have not been established in patients with mild to moderate hepatic impairment therefore perindopril arginine and amlodipine (as besylate) combination tablets should be administered with caution and treatment should start at the lower end of the dosing range (see PRECAUTIONS and PHARMACOLOGY, Pharmacokinetics and Metabolism sections). Dose adjustments can be made by decreasing or increasing the dose of either perindopril and/or amlodipine using separate perindopril and/or amlodipine products within the recommended dose range until an optimal starting and maintenance dose is found. Patients with hepatic insufficiency should be started on amlodipine 2.5 mg once daily.

OVERDOSAGE
There is no information on overdosage with perindopril arginine and amlodipine (as besylate) combination tablets in humans.

Symptoms
Related to Perindopril Component
Limited data are available for overdosage in humans.

Symptoms associated with overdosage of ACE inhibitors may include hypotension, circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety, and cough.

Related to Amlodipine Component
Available data suggest that overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly a reflex tachycardia. Dysrhythmias may occur following overdose with any calcium antagonists. Hypotension and bradycardia are usually seen within 1 to 5 hours following overdose. Hypotension can persist for longer than 24 hours despite treatment. Cardiac rhythm disturbances have been noted to persist for up to 7 days. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome have been reported.

Treatment
Related to Perindopril Component
The recommended treatment of overdosage is intravenous infusion of normal saline solution. If hypotension occurs, the patient should be placed in the shock position. If available, treatment with intravenous catecholamines may also be considered. Perindopril may be removed from the general circulation by haemodialysis (see PRECAUTIONS). Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.
Related to Amlodipine Component
If massive overdose should occur, active cardiac and respiratory monitoring should be instituted. Frequent blood pressure measurements are essential. Should hypotension occur, cardiovascular support including elevation of the extremities and the judicious administration of fluids should be initiated. If hypotension remains unresponsive to these conservative measures, administration of vasopressors (such as phenylephrine), should be considered with attention to circulating volume and urine output. Intravenous calcium may help to reverse the effects of calcium entry blockade. Administration of activated charcoal to healthy volunteers immediately or up to 2 hours after ingestion of amlodipine 10mg has been shown to significantly decrease amlodipine absorption. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via nasogastric tube once the airway is protected. Ipecac-emesis is not recommended since haemodynamic instability and CNS depression may rapidly develop. Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

PRESENTATION AND STORAGE CONDITIONS
APO-Perindopril Arginine/Amlodipine 5/5, 5/10, 10/5 & 10/10 Tablets are intended for oral administration.

Each tablet contains perindopril arginine and amlodipine (as besylate) respectively: 5mg/5mg, 5mg/10mg, 10mg/5mg & 10mg/10mg as the active ingredient.

5mg/5mg Tablet
White to off-white coloured, oval-shaped biconvex tablets engraved with “APO” on one side and “5/5” on the other side.
Bottle (round HDPE bottle with child-resistant cap and desiccant) of 30 tablets. AUST R 224306.
Blister (Aluminium/Aluminium silver foil) of 30 tablets. AUST R 224333.

5mg/10mg Tablet
White to off-white coloured, square-shaped biconvex tablets engraved with “APO” on one side and “5/10” on the other side.
Bottle (round HDPE bottle with child-resistant cap and desiccant) of 30 tablets. AUST R 224292.
Blister (Aluminium/Aluminium silver foil) of 30 tablets. AUST R 224325.

10mg/5mg Tablet
White to off-white coloured, triangular-shaped biconvex tablets engraved with “APO” on one side and “10/5” on the other side.
Bottle (round HDPE bottle with child-resistant cap and desiccant) of 30 tablets. AUST R 224316.
Blister (Aluminium/Aluminium silver foil) of 30 tablets. AUST R 224309.

10mg/10mg Tablet
White to off-white coloured, round-shaped biconvex tablets engraved with “APO” on one side and “10/10” on the other side.
Bottle (round HDPE bottle with child-resistant cap and desiccant) of 30 tablets. AUST R 224300.
Blister (Aluminium/Aluminium silver foil) of 30 tablets. AUST R 224312.

Not all strengths and/or pack types may be available.

Storage
Store below 25°C. Keep container tightly closed. Protect from moisture. Protect from Light.

NAME AND ADDRESS OF THE SPONSOR
Apotex Pty Ltd
16 Giffnock Avenue
Macquarie Park  NSW  2113

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POISON SCHEDULE OF THE MEDICINE
S4 – Prescription Only Medicine.

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG):
12 January 2016